Existing cardiomyocytes generate cardiomyocytes at a low rate after birth in mice.

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Authors: Shah R Ali, Simon Hippenmeyer, Lily V Saadat, Liqun Luo, Irving L Weissman, Reza Ardehali

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Public Summary:
We generated two novel models for this study using the latest version of the sophisticated “mosaic analysis of double markers” (MADM) mouse model, in which asymmetric, indelible labeling of two daughter cells enables elucidation of precursor-progeny relationships. Unique to this system, only cells that arise from mitosis become achieve a specific label, so there is no ambiguity between newborn cells and cells that have undergone binucleation or DNA repair (a major limitation for cardiac assays that rely on proxies of division). The first model utilizes a cardiomyocyte-specific Cre (Myh6-CreERT2), and therefore only cardiomyocytes can undergo MADM recombination; only Myh6-expressing cardiomyocytes can be potential “parent” cells. In the second model (using ß-actin-CreER) any cell type can undergo MADM recombination, allowing us to elucidate contribution to postnatal cardiogenesis from putative progenitor cells. Using these novel models (this is the first demonstration of the elegant MADM system in the heart), we show that cardiomyocytes undergo symmetric division postnatally at a very low rate and we do not find any evidence of asymmetric division, self-renewal, or multi-lineage clones that would be characteristic of a progenitor cell. Further, we do not observe that a myocardial infarction injury increases the global rate of cardiomyocyte generation. Importantly, because MADM labeling can only occur in the setting of concomitant Myh6 expression, our data excludes possible dedifferentiation of cardiomyocytes to progenitor cells prior to division (one of the arguments potentially raised against the zebrafish studies that demonstrate a cardiomyocyte origin of post-injury regeneration using lineage tracing, which only relies on the historical expression of cardiomyocyte-associated genes).

Scientific Abstract:
The mammalian heart has long been considered a postmitotic organ, implying that the total number of cardiomyocytes is set at birth. Analysis of cell division in the mammalian heart is complicated by cardiomyocyte binucleation shortly after birth, which makes it challenging to interpret traditional assays of cell turnover [Laflamme MA, Murray CE (2011) Nature 473(7347):326-335; Bergmann O, et al. (2009) Science 324(5923):98-102]. An elegant multi-isotope imaging-mass spectrometry technique recently calculated the low, discrete rate of cardiomyocyte generation in mice [Senyo SE, et al. (2013) Nature 493(7432):433-436], yet our cellular-level understanding of postnatal cardiomyogenesis remains limited. Herein, we provide a new line of evidence for the differentiated alpha-myosin heavy chain-expressing cardiomyocyte as the cell of origin of postnatal cardiomyogenesis using the "mosaic analysis with double markers" mouse model. We show limited, life-long, symmetric division of cardiomyocytes as a rare event that is evident in utero but significantly diminishes after the first month of life in mice; daughter cardiomyocytes divide very seldom, which this study is the first to demonstrate, to our knowledge. Furthermore, ligation of the left anterior descending coronary artery, which causes a myocardial infarction in the mosaic analysis with double-marker mice, did not increase the rate of cardiomyocyte division above the basal level for up to 4 wk after the injury. The clonal analysis described here provides direct evidence of postnatal mammalian cardiomyogenesis.

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